The Applicants respectfully submit that the hypothetical combination of Kantlehner and Rajopadhye with Scheibler does not result in a cyclopeptide with both a cell targeting molecule and a diagnostic or therapeutic molecule on each of its two faces. Indeed, the rejection relies upon Scheibler for teaching the homodetic cyclopeptide. However, Scheibler does not permit modification of the cyclopeptide to include functional groups on each face.

Scheibler discloses a molecular thin film of RAFT molecules grafted to a gold surface on one face and an antigenic peptide on the other face. The reason is to functionalize a gold or other surface, thus teaching against free RAFT molecules. Due to this the final grafted cyclopeptides have only one face available for grafting to additional functional molecules.

Consequently, one skilled in the art hypothetically motivated to include a recognition molecule or a diagnostic molecule would be required to select only one agent and leave the bond between the cyclopeptide and the gold surface intact. Indeed, if Scheibler's molecular thin film were modified to have a peptide derived from cyclo-(RGDfK) on one face and a detection agent on the other face, the configuration would not permit further grafting to the gold surface, thereby rendering Scheibler's film unsatisfactory for its intended purpose.

According to MPEP §2143.01V, there can be no suggestion or motivation to make a proposed modification if such a modification would render the prior art invention inoperable for its intended purpose. Therefore, the Applicants respectfully submit that a homodetic cyclopeptide comprising the peptide derived from cyclo-(RGDfK) on one face and a detection agent on the other face cannot be obvious in view of Scheibler alone or in combination with Kantlehner and Rajopadhye.

Furthermore, Scheibler, Kantlehner, and Rajopadhye do not suggest the unexpected result of enhanced cell-targeting of the recognition molecule grafted to a cyclopeptide compared to the recognition molecule alone. Indeed, a post-filing publication co-authored by the inventors demonstrates that RAFT(cRGD) conjugates have improved cell-targeting capabilities and that spatial separation of the targeting and therapeutic domains is important to reduce the risk that one domain will sterically hinder the accessibility of the other domain. (See enclosed, Garanger, 2005, "New multifunctional molecular conjugate vectors for targeting, imaging, and therapy of tumors. Molecular Therapy," 12(6):1168-75).

The Applicants also enclose:

1) D. Boturyn, J.-L. Coll, E. Garanger, M.-C. Favrot, P. Dumy. Template Assembled Cylopeptides as Multimeric System for Integrin Targeting and Endocytosis. *J. Am. Chem. Soc.*, **2004**, *126*, 5730-5739.

This article discloses the claimed cyclopeptide grafted on both faces (Fig. 1). One face of the cyclopeptide comprises 4 RGDfK (the recognition molecule) and the other face a labeling. The method for producing the cyclopeptide is the same as that claimed and the article discloses that the choice of glycine for the cyclization step prevents racemization of the cyclopeptide. This step is important to have both faces of the cyclopeptide functionalized (Page 5732, Col. 2, Lines 31-33).

2) E. Garanger, D. Boturyn, Z. Jin, P. Dumy, M.-C. Favrot, J.-L. Coll. New multifunctional molecular conjugate vector for targeting, imaging and therapy of tumors, *Molecular Ther.*, **2005**, *12*, 1168-1175.

This article, as mentioned above, discloses the cyclopeptide grated on one face with 4 RGDfK and on the other face with a labeling molecule. The article clearly indicates that the spatial separation between the targeting and the drug delivery domains is important to reduce the risk that the one domain sterically affects the conformation and accessibility of the other one (Page 1168, Col. 2, Lines 1-7). The article discloses the effectiveness of cells targeting and that cells targeting with the grafted recognition molecule cyclopeptide are enhanced compared to the recognition molecule alone.

3) E. Garanger, D. Boturyn, J.-L. Coll, M.-C. Favrot, P. Dumy. Multivalent RGD synthetic peptides as potent $\alpha V\beta 3$ integrin ligands. *Org. Biomol. Chem.*, **2006**, *4*, 1958-1965.

This article discloses a study of the binding effect with regard to the number of grafted RGD molecules on one face of the cyclopeptide.

4) Z. Jin, V. Josserand, J. Razkin, E. Garanger, D. Boturyn, M.-C. Favrot, P. Dumy, J.-L. Coll. Non-invasive optical imaging of ovarian metastases using Cy5-labeled RAFT-c(-RGDfK-)4. *Molecular Imaging*, **2006**, *5*, 188-197.

5) J. Razkin, V. Josserand, D. Boturyn, Z. Jin, P. Dumy, M. Favrot, J.-L. Col, I. Texier. Activatable fluorescent probes for tumour-targeting imaging in live mice. *Chem. Med. Chem.*, **2006**, *1*, 1069-1072.

6) Z. Jin, J. Razkin, V. Josserand, D. Boturyn, A. Grichine, I. Texier, M.-C. Favrot, P. Dumy, J.-L. coll. *In vivo* non-invasive optical imaging of receptor-mediated RGD internalization using self-quenched Cy5-labeled RAFT-c(-RGDfK-)4. *Molecular Imaging*, **2007**, *6*, 43-55.

The three above articles show the use of a both faces grafted cyclopeptide with one face having RGD molecules and on the other face a labeling molecule for imaging.

All of the above articles show the claimed cyclopeptide grafted on one face with the recognition molecule, but the other face of the cyclopeptide is not grafted with a therapeutic molecule but only with a recognition molecule. The articles thus reveals that the use of the cyclopeptide grafted with RGDfK and labeling molecule achieves better recognition for the tumor targeting than the labeled RGDfK alone, i.e., without the cyclopeptide.

The above articles also reveal that the claimed grafted cyclopeptide can be internalized in the cells and directly delivers the therapeutic molecule grafted on the other face of the cyclopeptide directly into the cells.

In summary, the Applicants respectfully submit that:

- the use of glycine to prepare the cyclopeptide causes a controlled face functionalization of the cyclopeptide --- which is not disclosed in the cited publications;

- none of the cited publications suggests a cyclopeptide having both cell targeting (on one face) and a therapeutic or diagnostic molecule (on the other face);

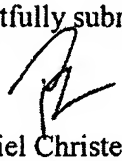
- none of the cited publications suggest that the use of a grafted cyclopeptide will result in better tumour imaging; and

- in Sheiber, the cyclopeptide is grafted on a gold surface with a thioalkane linker and after grafting the cyclopeptide, a peptide is grafted onto the exposed free face of the cyclopeptide (the final grafted cyclopeptide is not free in solution).

Based on the foregoing, the Applicants respectfully submit that the subject matter of the rejected claims is non-obvious in view of the hypothetical combination of Scheibler, Kantlehner, and Rajopadhye. Accordingly, removal of the rejection under 35 U.S.C. §103 is respectfully requested.

The Applicants respectfully submit that the entire application is now in condition for allowance, which is respectfully requested.

Respectfully submitted,



T. Daniel Christenbury
Reg. No. 31,750
Attorney for Applicants

TDC/LML/as
(215) 656-3381